REMARKS

The Present Invention

The present invention provides for novel heterocyclic dihydropyrimidine compounds, pharmaceutical compositions containing such compounds and methods of using such compounds as inhibitors of ion channel function.

Amendments to the Claims

New claims 91-96 have been added. New claims 91-95 are directed to compounds of the present invention that are effective as inhibitors of ion channel function. New claim 96 is directed to compositions containing compounds of the present invention. Claims 62 and 82 have been amended to correct typographical errors. Claim 82 has also been amended to exclude non-elected subject matter. The new claims and amendments correct typographical errors and/or contain matter that may be found in the specification as originally filed, for example, at page 11, line 5 to page 13, line 14, the Examples and the original claims. Accordingly, no new matter has been added by way of the aforesaid new claims and amendments.

The Pending Claims

Claims 61-63, 66-68, 78, 81-85 and 91-96 are now pending in this application. Claims 64, 65 and 80 have been withdrawn from consideration in view of a restriction requirement. In an Advisory Action dated July 15, 2005, it was noted that claims 86-90 (now new claims 91-95) set forth in applicants' response to the Final Rejection dated April 25, 2005 filed on June 27, 2005 were not entered because they would raise new issues that would require further consideration. Claims 61-63, 66-68, 78, 81-85 and 91-96 provide for novel heterocyclic compounds, pharmaceutical compositions containing such compounds and methods of using of such compounds as inhibitors of ion channel function.

The Office Action

In the Office Action dated December 2, 2005, claims 61-63, 66-68, 78 and 81-85 were rejected under 35 U.S.C. §103(a) for allegedly being unpatentable in view of the prior art.

Rejection under 35 USC § 103

Claims 61-63, 66-68, 78 and 81-85 stand rejected under 35 U.S.C. §103(a) for allegedly being unpatentable over Tsuda et al. (European Patent EP 0217142). As indicated in applicants' Response to Office Action filed on December 16, 2004, which is incorporated herein as if set forth at length, applicants respectfully traverse the Section 103 rejection on the grounds that the Office Action has not established a proper *prima facie* case of obviousness.

The U.S.P.T.O. has the initial burden of demonstrating why one skilled in the art would have been motivated to make the proposed modifications needed to arrive at the presently claimed compounds. The Office Action contends that the rejected claims recite specific species that are not disclosed in Tsuda et al. but yet fall within the scope of a larger genus in Tsuda et al. and, as a result, the present claims are *prima facie* obvious over Tsuda et al.. Applicants respectfully submit that, as pointed out above, the compounds defined by the present claims do not fall within the scope of Tsuda et al.'s disclosure. As set forth in applicants' Response to Office Action filed on December 16, 2004, which is incorporated herein as if set forth at length, Tsuda et al. lists over 800 compounds that are different from the compounds of the present invention. As set forth in applicants' Response to Office Action filed on December 16, 2004, which is incorporated herein as if set forth at length, there is no teaching or suggestion for further experimentation to derive the claimed compounds. The Examiner's position is based on the Examiner's stated genus-species relationship. However, the Federal Circuit has clearly state that this position, alone, does not establish a *prima facie* case of obviousness. For example, in *In re Jones*, 21 USPQ2d 1941 (Fed. Cir. 1992), the court specifically said that this position both in that case and here is insufficient:

> We decline to extract from Merck the rule that the Solicitor appears to suggest—that regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it....Conspicuously missing from this record is any evidence, other than the PTO's speculation (if it can be called evidence) that one of ordinary skill in the herbicidal art would have been motivated to make the modifications of the prior art salts necessary to arrive at the claimed ... ethanol salt.

See *Jones*, *id* at page 1943.

Jones makes it clear that reliance solely on an asserted genus-species relationship is not sufficient, without more, to establish a *prima facie* case of obviousness.

In addition, the Office Action contends that the claimed compounds are structural analogs or homologs of the reference compounds, and contends at page 4, that it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the reference compounds to prepare the structural homologs, that one of ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally homologous compounds are expected to possess similar properties, and that holdings from two cases, one of which was decided in 1944 and the other in 1950 (namely, *In re Hass* and *In re Henze*, respectively) support a holding of *prima facie* obviousness.

Assuming, *arguendo*, that the Office Action accurately describes the recited reference and inventive compounds as structural analogs or homologs of one another, applicants respectfully submit that, in contrast to the Office Action's contention, recent case law provides clear support for the proposition that the mere recognition that an inventive compound is of the same general class as a prior art compound does not in and of itself constitute a case of *prima facie* obviousness. See *In re Lalu*, 223 USPQ 1257 (Fed.Cir.1984) (obviousness rejection reversed where the reference and inventive compounds are homologous); *Jones* (obviousness

rejection reversed where the reference and inventive compounds were salt variants of one another); and *In re Grabiak*, 226 USPQ 870 (Fed.Cir.1985) (obviousness rejection reversed where the reference and inventive compounds vary only in that one is an ether and the other a thioether). Similar to the arguments set forth above, in each case, the Court plainly instructs that an obvious to try rationale, which seems to be the suggested basis for the rejection, is not sufficient to establish *prima facie* obviousness under 35 U.S.C. § 103. There must be "some objective suggestion or teaching" in the prior art to modify the reference. See *Lalu*, 223 USPQ at 1259 ("[i]n determining whether a case of *prima facie* obviousness exists, it is necessary to ascertain whether the prior art teachings would appear to be sufficient to one of ordinary skill in the art to suggest making the claimed substitution or other modification."; also see *Jones*, 21 USPQ2d at 1943 ("Conspicuously missing from this record is any evidence, other than PTO's speculation … that one of ordinary skill in the herbicidal art would have been motivated to make modifications of the prior art salts necessary to arrive at the claimed [invention]."); and *Grabiak*, 226 USPQ at 872 ("there must be adequate support in the prior art for the ester/thioester change in structure in order to complete the PTO's prima facie case and shift the burden of going forward to the applicant.").

At page 4, the Office Action contends that the alleged structural similarity between certain of the claimed and reference compounds supports the obvious rejection. Similarly, the Office Action contends that the there is sufficient motivation for preparing the claimed compounds based on the expectation that an alleged structurally similar compound can have generally the same properties as another structurally similar compound. Applicants respectfully submit that recent case law makes it clear that such contentions are insufficient as support for a *prima facie* case of obviousness. As indicated above, recent case law makes it clear that, in contrast to the Office Action's contention, there most be some recital of an objective suggestion or teaching in the prior art to make the modifications set forth in the claims of the present invention. Applicants respectfully submit that no such recital of an objective suggestion or teaching in the prior art to make the modifications set forth in the claims of the present invention is provided in the Office Action.

In addition, applicants respectfully traverse the Section 103 rejection on the grounds that the cited reference does not support a *prima facie* case of obviousness of the present invention.

The Office Action contends that Tsuda et al. teaches compounds that are pyrazolo[1,5-a]pyrimidine compounds that are useful as pharmaceutical therapeutic compounds. However, one deficiency of Tsuda et al., as noted by the Office Action on page 3, is that Tsuda et al. fails to disclose or suggest specific species as set forth in the claims. Another deficiency of Tsuda et al. is that it fails to teach, disclose or suggest compounds that demonstrate activity other than Ca^{2+} activity.

Tsuda et al. describes compounds which exhibit Ca^{2+} activity. In contrast, the presently claimed compounds exhibit K_v1 activity, especially $K_v1.5$ activity. No where does Tsuda et al. teach or disclose that the compounds can exhibit activity other than Ca^{2+} activity let alone $K_v1.5$ activity. The $K_v1.5$ activity of the presently claimed compounds is important and has practical working advantages in that the $K_v1.5$ activity allows for treatment of specific types of arrhythmias, for example atrial arrhythmias, because $K_v1.5$ is expressed in the atrium not the ventricle (see page 6, line 29 to page 7.line 28). While Tsuda et al. does disclose the use of the compounds to treat arrhythmia generically, it does not teach or disclose that the compounds would be particularly effective in treating atrial arrhythmia rather than ventricular arrhythmia as presently claimed. In addition, Tsuda et al. fails to suggest or disclose the unexpected benefits that are believed to be associated with the use of $K_v1.5$ inhibitors in treating atrial arrhythmia (for example, lack of pro-arrhythmic side effects associate with other known therapies, see page 4, line 13 to page 7, line 28.).

Therefore, for the reasons set forth above, Tsuda et al. does not support a Section 103 rejection.

In view of the foregoing, applicants respectfully submit that the presently rejected claims are unobvious and patentable over the prior art. Accordingly, applicants respectfully request the withdrawal of the above-discussed Section 103 rejections.

Conclusion

The presently submitted amendment and remarks are believed to be fully responsive to the rejection noted in the outstanding Office Action. Accordingly, applicants respectfully submit that the pending claims are in condition for allowance. An early Office Action to that effect is, therefore, earnestly requested.

The Commissioner is hereby authorized to charge any fees that may be required, including any fees under 37 C.F.R. §§1.16 and 1.17, for the filing of this paper to Deposit Account No. 19-3880.

If, in the opinion of the Examiner, a telephone conference with the undersigned would facilitate prosecution of this patent application, the Examiner's call would be welcomed.

Respectfully submitted,

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